REMARKS

Claims 1 – 3, 23 – 25 and 50 - 51 are pending in the application. Claims 2, 4 – 22 and 24 – 51 have been cancelled as being drawn to non-elected subject matter. Claims 1 and 23have been amended.

No new matter has been added by virtue of these amendments; support therefore can be found in throughout the specification and original claims of the application.

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Applicants note that in the Advisory Action mailed on November 3, 2008, the Examiner has indicated that Applicant's argument presented above has overcome the rejections raised under 35 USC 112 over claims 1 – 3 and 23 – 24.

Objections

Drawings

The Examiner argues that the drawings filed on 5/05/2005 are objected to under 37 CFR 1.83(a) because "they fail to show the specific details as disclosed in the brief description on pages 4 – 7 of the specification." (Office Action, p.2).

Applicants are submitting replacement drawings with the present response.

Rejection of Claims 1 - 3 and 23 – 25 Under 35 USC 112, First Paragraph
Written Description

Claims 1 – 3 have been rejected under 35 USC 112, first paragraph for allegedly failing to comply with the written description requirement. The Examiner argues that the claims contain subject matter that was not described in the specification in such a way

to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

As pointed out by the Examiner, the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by "...**disclosure of relevant identifying characteristics, i.e., structure** or other physical and/or chemical properties, by functional characteristics **coupled with a known or disclosed correlation between function and structure**, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus."

The claims are drawn to method of killing a tumor cell using a genus of siRNAs that are at least 95% identical to SEQ ID NO: 4, and that are specific for a DNA repair protein.

The specification teaches actual reduction to practice of siRNAs that encode a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4. As pointed out by the Examiner, Figure 15 depicts the sequences of the oligonucleotides used to construct the ATM-2 siRNA-encoding nucleic acid molecules, including SEQ ID NO: 4. The specification teaches using the siRNA constructs of the instant invention for down-regulation of DNA repair proteins, including ATM, for example starting at paragraph [0138] and further teaches siRNA silencing of repair proteins using the siRNAs taught in the instant invention to render tumor cells sensitive to DNA-damaging Agents [0140]. There are certain art-recognized correlations between siRNA function and the structure of the target that would aid the selection of those fragments having antisense activity, and, accordingly, the structure of all possible siRNAs that are at least 95% identical to SEQ ID NO: 4 can be predicted from SEQ ID NO: 4.

Example 14 of the Written Description Guidelines Training Materials illustrates the application of the written description requirement to the following generic claim:

> A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A → B.

Under the Training Materials, a generic claim similar to Example 14 would be adequately described under Section 112, ¶ 1, because (1) "[t]he single species

disclosed is *representative of the genus* because all members have at least 95% structural identity with the reference compound," and (2) because of the limitation requiring the stated compounds to catalyze the reaction of A → B. See Training Materials at 54. (Emphasis added).

Likewise, the instant claims are directed to siRNA is encoded by a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4 and at least one DNA-damaging agent and wherein the siRNA and the at least one DNA damaging agent kill a tumor cell.

Accordingly, based on the Guidelines, the instant claims satisfy the written description requirement and, therefore, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection

Given the high level of skill in the siRNA art, those of ordinary skill in the art would consider the applicant to have been in possession of the entire breadth of the claimed genus of siRNAs based on the teachings of the disclosure.

Applicants respectfully request that the rejection be withdrawn.

Rejection of Claims 1 - 3 and 23 – 25 Under 35 USC 112, First Paragraph Enablement

The rejection of claims 1 - 3 and 23 – 25 under 35 USC 112, first paragraph for allegedly failing to comply with the enablement requirement has been maintained by the Examiner. The Examiner argues that the claims, while being enabling for a method of killing a tumor cell in vitro comprising contacting the cell in vitro with a small inhibitory RNA specific for a DNA repair protein and at least one DNA-damaging agent, does not reasonably provide enablement for a method of killing a tumor cell comprising contacting the cell in vivo with a siRNA specific for a DNA repair protein and at least one DNA-damaging agent. Applicants respectfully traverse this rejection.

The instant claims recite a method of killing a tumor cell comprising contacting the cell with at least one small inhibitory RNA (siRNA), wherein the siRNA is encoded by a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4 and at least one DNA-damaging agent, wherein the siRNA encoded by the nucleic acid molecule is specific for the DNA repair protein ATM, and wherein the siRNA and the at least one DNA damaging agent kill a tumor cell. The claims also recite a method of treating a

subject having cancer comprising administering to the subject a therapeutically effective amount of at least one small inhibitory RNA (siRNA) specific for a DNA repair protein and a therapeutically effective amount of at least one DNA-damaging agent, wherein the siRNA encoded by the nucleic acid molecule is specific for the DNA repair protein ATM.

The instant invention demonstrates the first use of siRNA to augment radiation-mediated killing of human cancer cells and highlights the use of siRNA as an adjuvant gene therapy strategy to radiation and chemotherapy. Where DNA repair proteins, in particular the repair proteins ATM, ATR and DNA-PK, are the target, siRNA was designed for each target complimentary to three different regions of the corresponding mRNA at increasing distance from the AUG translation initiation codon, and the resulting constructs were then screened for their ability to down-regulate target protein expression.

The Examiner argues that the level of unpredictablity in the art for therapeutic in vivo applications is high, and without a working embodiment, the specification does not provide enough guidance to enable one of skill in the art to make and/or use the claimed invention.

Applicants again point out that the specification provides detailed teachings regarding the methods in order to enable the claimed invention. However, solely in the interest of advancing prosecution, applicants have amended the claims to recite that the siRNA is encoded by the nucleic acid molecule specific for the DNA repair protein ATM.

Accordingly, the specification enables the claims as now pending. In particular, the specification teaches that

Applicants point out that at paragraph [0078], the specification teaches that with respect to the methods of the invention:

> target cancer cells (i.e., neoplastic, proliferative cells) are contacted with an appropriate siRNA vector described herein (preferably in the form of an adenovirus) such that the vector enters the cell and expression of the siRNA is induced. The target cancer cells are further exposed to a DNA-damaging agent (e.g., radiation and/or chemotherapeutic agent(s)).

The specification then teaches step by step how methods of the invention would

be carried out.

First, the specification teaches that the siRNAs of the invention can be targeted to any DNA repair protein. The Application teaches the target and possible sequences of the siRNAs, for example at paragraph [0081], as pointed out in a previous response.

At paragraph [0094], the specification clearly teaches how to isolate nucleic acids that encode the siRNAs used in the method of the invention. The specification teaches at [0096] that standard techniques, e.g. "techniques for isolating mRNA, purifying and analyzing nucleic acids, methods for making recombinant vector DNA" are well known in the field. At paragraphs [0098] – [0100] the specification teaches how to construct nucleic acid molecules of the invention, how to isolate the nucleic acid molecules using synthetic oligonucleotide primers designed based upon the sequences disclosed, and how to produce the siRNAs of the invention by inserting a double-stranded DNA molecule that encodes the siRNA into an expression vector.

Additionally, the specification teaches how to deliver the adenoviral vectors to the target cell. For example, at [0091], where the specification teaches that "adenoviral vectors may be delivered to the target cell in a variety of ways, including, but not limited to, liposomes, general transfection methods that are well known in the art (such as calcium phosphate precipitation or electroporation), direct injection, and intravenous infusion."

As pointed out previously, the specification sets forth at [0086] -- [0093] dosage and administration of the adenoviral vectors to the target cell. At [0086], the specification describes dosage levels and schedules. The specification partiuclarly teaches at [0088] tumor cells that can be targeted by the methods of the invention:

> The methods of the invention are intended to be used for any type of tumor, cancer, and/or neoplasm, including, but not limited to, those derived from prostate, colon, breast, lung, brain, skin, ovary, pancreas, liver, stomach, bladder, bone, testicle, uterus, adipose tissue, throat, kidney, tongue, pituitary gland, thyroid, nerve, lymphoid tissue, eye, and/or cervix. Additionally, the methods of the invention are intended to be used for tumors which may be a mixture of more than one cell type, as well as for metastasized tumors which are originally derived from one cell type, but have migrated to a different part of the body.

In addition to the methodology for performing the invention described above, the specification provides teaching for killing a tumor cell comprising contacting the cell in with a siRNA specific for a DNA repair protein, wherein the protein in ATM, and at least one DNA-damaging agent. In Example 1, the specification describes enhanced radiation and chemotherapy-mediated cell killing of human cancer cells by small inhibitory RNA silencing of DNA repair factors, including ATM. In particular, the specification teaches how to design siRNAs to target ATM, for example at paragraph [0127] of the disclosure where "siRNAs were designed to target nucleotides 223-253 (G/C content=45%), 432-462 (G/C content=55%), and 597-627 (G/C content=42%) of the ATM mRNA (GenBank Accession No. U33841)." Applicants teach that "initial screening of siRNA for their effectiveness showed that all three target proteins were down-regulated by 90% from 24- to 72-h post-transfection (FIG. 1), with protein levels being comparable with the levels seen in untransfected and vector-transfected cells at 96 h (and that) these findings are consistent with previous data reporting the half-lives of these proteins to be in the region of 24-48." (paragraph [0147]). The specification teaches that siRNA-mediated inhibition in the expression of DNA repair proteins confers an increased sensitivity to therapeutically relevant DNA-damaging agents (FIGS. 2 and 3).

Accordingly, the specification as filed enables one of skill in the art to make and/or use the invention as claimed. Applicants respectfully request that the rejection be withdrawn.

Rejection of Claim 1 Under 35 USC 103(a)

The rejection of claim 1 under 35 U.S.C. § 103(a) as being unpatentable over Fan et al. (Cancer Gene Therapy 2000, Vol. 7, No. 10: 1307 – 1314), in view of Hammond et al. and Tuschl et al. (WO 02/44321) is maintained by the Examiner. Applicants respectfully traverse the rejection.

Claim 1 recites a method of killing a tumor cell comprising contacting the cell with at least one small inhibitory RNA (siRNA), wherein the siRNA is encoded by a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4 and at least one DNA-damaging agent, wherein the siRNA encoded by the nucleic acid molecule is specific

for the DNA repair protein ATM, and wherein the siRNA and DNA damaging agent kill a tumor cell.

The Fan et al. reference fails to teach or suggest all the elements of the instant invention. In particular, the Fan reference does not teach or suggest contacting the cell with at least one **small inhibitory RNA (siRNA)**, wherein the siRNA is encoded by a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4 and at least one DNA-damaging agent, wherein the siRNA and DNA damaging agent kill a tumor cell. Nowhere in the Fan reference is there teaching or suggestion of SEQ ID NO: 4 or a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4.

The Examiner argues that the Fan reference teaches generation of an antisense molecule from the transcriptional start domain of the human ATM gene having nucleotides 188 to 445 which comprises nucleotides 395 to 445 of SEQ ID NO: 4. (Office Action, p.7). The Fan reference teaches that **cDNA fragments containing either the translational start domain (188 – 445 bp), the PI-3K domain (8167 – 8854) or both** of these domains of the ATM gene were cloned in an antisense orientation from the CMV promoter in an adenovirus plasmid, and then cotransfected into cells. Nowhere does the Fan reference teach or suggest **siRNA that is encoded by a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4** as taught by the instant claims. **All siRNAs that are complementary to the ATM target mRNA sequence will not have gene silencing effects.**

The claims are directed to specific siRNA molecules that are encoded by nucleic acid molecules that are at least 95% identical to SEQ ID NO: 4 and have gene silencing activity.

First Applicants point out again that antisense and siRNA are **two different, non-analogous methodologies** for silencing gene expression.

The specification teaches at paragrapn [0147] that "siRNAs were designed to target nucleotides 223-253 (G/C content=45%), 432-462 (G/C content=55%), and 597-627 (G/C content=42%) of the ATM mRNA (GenBank Accession No. U33841)."

It is not known if any siRNA to any target sequence in the ATM gene between nucleotides 188 – 445 would have gene silencing effects. Nowhere does the Fan reference teach or suggest use of siRNA silencing and nowhere does Fan teach or

suggest silencing of the nucleic acids encompassed by SEQ ID NO: 4 or a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4.

Neither of the Hammond nor the Tuschl references cure the defects of the Fan reference. Nowhere in either of the Hammond or the Tuschl references is there teaching or suggestion of the specific sequence set forth as SEQ ID NO:4. Therefore, the teachings of the cited art, when combined, do not result in the claimed invention.

Accordingly, Applicants request that the rejection be withdrawn.

Early consideration and allowance of the application are earnestly solicited.

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Respectfully submitted,

By _____

Customer Number 49383

Jonathan M. Sparks, Ph.D.
Registration No.: 53,624
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 439-4444
Attorneys/Agents For Applicant